Introduction to Organic Reactions

- In general, we look at what occurs and try to learn how it happens
- Common patterns describe the changes
  - Addition reactions – two molecules combine
  - Elimination reactions – one molecule splits into two
  - Substitution – parts from two molecules exchange
  - Rearrangement reactions – a molecule undergoes changes in the way its atoms are connected

6.2 How Organic Reactions Occur: Mechanisms

- In a clock the hands move but the *mechanism* behind the face is what causes the movement
- In an organic reaction, we see the transformation that has occurred. The mechanism describes the steps behind the changes that we can observe
- Reactions occur in defined steps that lead from reactant to product

Steps in Mechanisms

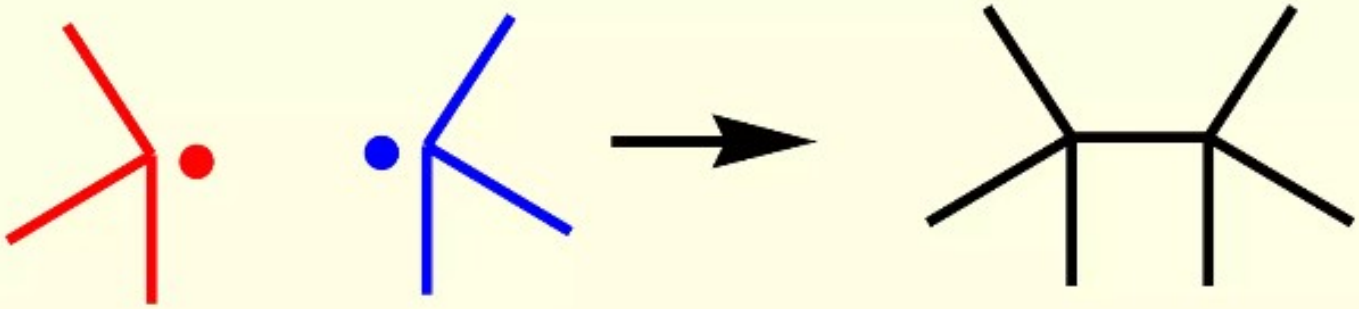
- We classify the types of steps in a sequence
- A step involves either the formation or breaking of a covalent bond
- Steps can occur in individually or in combination with other steps
- When several steps occur at the same time they are said to be *concerted*

Types of Steps in Reaction Mechanisms

- Formation of a covalent bond
  - Homogenic or heterogenic
- Breaking of a covalent bond
  - Homogenic or heterogenic
- Oxidation of a functional group
- Reduction of a functional group

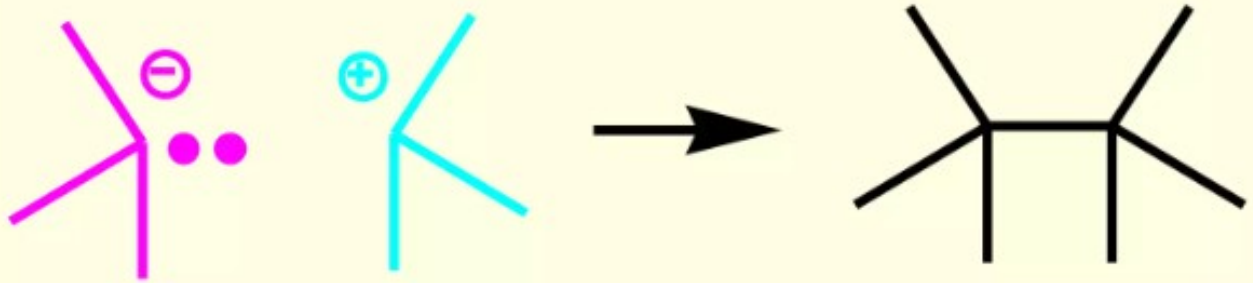
Homogenic Formation of a Bond

- One electron comes from each fragment
- No electronic charges are involved
- Not common in organic chemistry



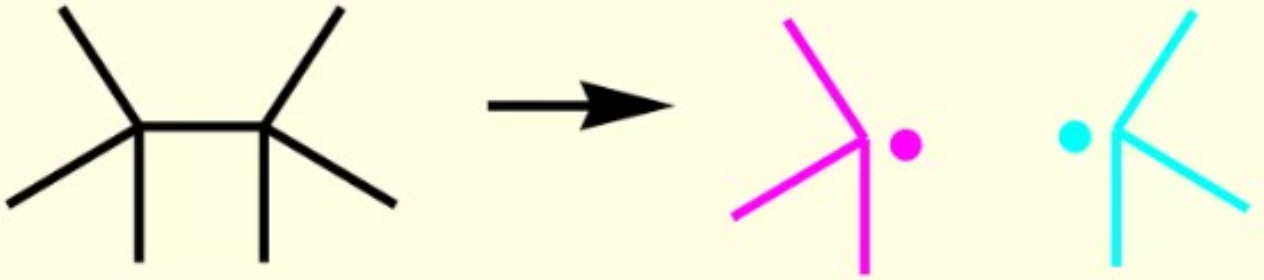
Heterogenic Formation of a Bond

- One fragment supplies two electrons
- One fragment supplies no electrons
- Combination can involve electronic charges
- Common in organic chemistry



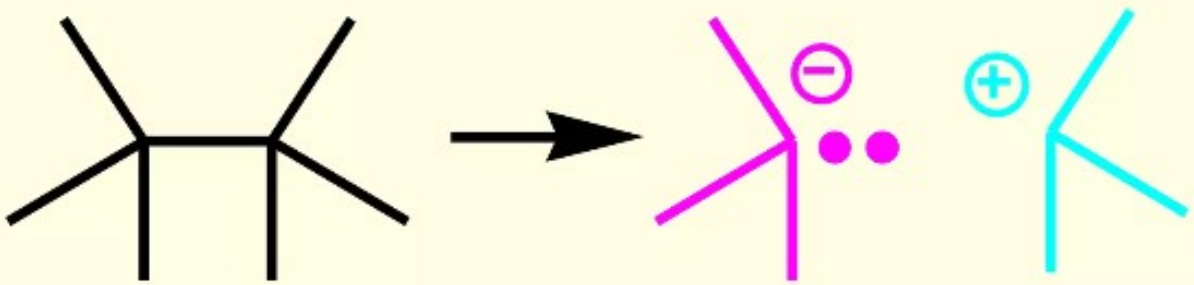
Homolytic Breaking of Covalent Bonds

- Each product gets one electron from the bond
- Not common in organic chemistry



Heterolytic Breaking of Covalent Bonds

- Both electrons from the bond that is broken become associated with one resulting fragment
- A common pattern in reaction mechanisms



Indicating Steps in Mechanisms

- Curved arrows indicate breaking and forming of bonds
- Arrowheads with a “half” head (“fish-hook”) indicate homolytic and homogenic steps (called ‘radical processes’)
- Arrowheads with a complete head indicate heterolytic and heterogenic steps (called ‘polar processes’)

Radicals

- Alkyl groups are abbreviate "R" for radical
  - Example: *Methyl* iodide = CH_3I, *Ethyl* iodide = CH_3CH_2I, *Alkyl* iodides (in general) = RI
- A "free radical" is an "R" group on its own:
  - CH_3 is a "free radical" or simply "radical"
  - Has a single unpaired electron, shown as: $CH_3^{\cdot}$
  - Its valence shell is one electron short of being complete

6.3 Radical Reactions and How They Occur

- Note: Polar reactions are more common
- Radicals react to complete electron octet of valence shell
  - A radical can break a bond in another molecule and abstract a partner with an electron, giving substitution in the original molecule
  - A radical can *add* to an alkene to give a new radical, causing an addition reaction

Steps in Radical Substitution

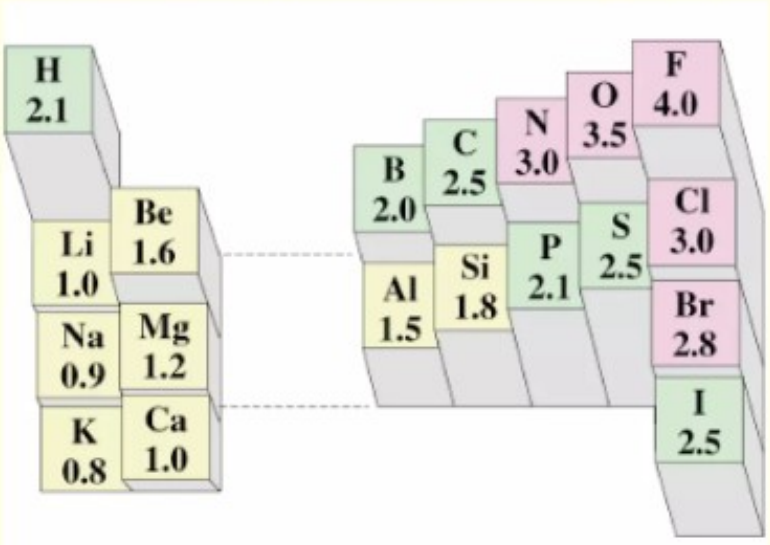
- Three types of steps
  - Initiation – homolytic formation of two reactive species with unpaired electrons
    - Example – formation of Cl atoms form Cl_2 and light
  - Propagation – reaction with molecule to generate radical
    - Example - reaction of chlorine atom with methane to give HCl and $CH_3^{\cdot}$
  - Termination – combination of two radicals to form a stable product: $CH_3^{\cdot} + CH_3^{\cdot} \rightarrow CH_3CH_3$

6.4 Polar Reactions and How They Occur

- Molecules can contain local unsymmetrical electron distributions due to differences in electronegativities
- This causes a partial negative charge on an atom and a compensating partial positive charge on an adjacent atom
- The more electronegative atom has the greater electron density

Electronegativity of Some Common Elements

- The relative electronegativity is indicated
- Higher numbers indicate greater electronegativity
- Carbon bonded to a more electronegative element has a partial positive charge (δ+)



Polarizability

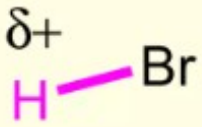
- Polarization is a change in electron distribution as a response to change in electronic nature of the surroundings
- Polarizability is the tendency to undergo polarization
- Polar reactions occur between regions of high electron density and regions of low electron density

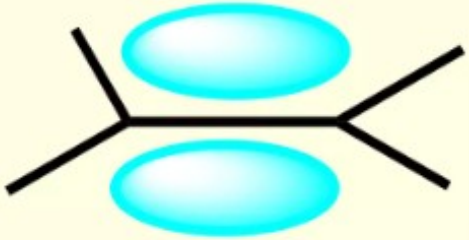
Generalized Polar Reactions

- An **electrophile**, an electron-poor species, combines with a **nucleophile**, an electron-rich species
- An electrophile is a Lewis acid
- A nucleophile is a Lewis base
- The combination is indicate with a curved arrow from nucleophile to electrophile

6.5 An Example of a Polar Reaction: Addition of HBr to Ethylene

- HBr adds to the π part of C-C double bond
- The π bond is electron-rich, allowing it to function as a nucleophile
- H-Br is electron deficient at the H since Br is much more electronegative, making HBr an electrophile





Mechanism of Addition of HBr to Ethylene

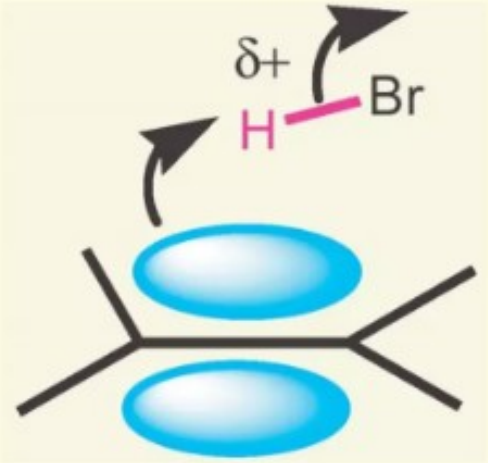
- HBr electrophile is attacked by π electrons of ethylene (nucleophile) to form a carbocation intermediate and bromide ion
- Bromide adds to the positive center of the **carbocation**, which is an electrophile, forming a C-Br σ bond
- The result is that ethylene and HBr combine to form bromoethane
- All polar reactions occur by combination of an electron-rich site of a nucleophile and an electron-deficient site of an electrophile

6.6 Using Curved Arrows in Polar Reaction Mechanisms

- Curved arrows are a way to keep track of changes in bonding in polar reaction
- The arrows track “electron movement”
- Electrons always move in pairs
- Charges change during the reaction
- One curved arrow corresponds to one step in a reaction mechanism

Rules for Using Curved Arrows

- The arrow goes from the nucleophilic reaction site to the electrophilic reaction site
- The nucleophilic site can be neutral or negatively charged
- The electrophilic site can be neutral or positively charged



Changes in Energy

- Free energy changes (ΔG°) can be divided into
  - a temperature-independent part called **entropy** (ΔS°) that measures the change in the amount of disorder in the system
  - a temperature-dependent part called **enthalpy** (ΔH°) that is associated with heat given off (exothermic) or absorbed (endothermic)

6.8 Describing a Reaction: Bond Dissociation Energies

- Bond dissociation energy (***D***): Heat change that occurs when a bond is broken by homolysis
- The energy is mostly determined by the type of bond, independent of the molecule
  - The C-H bond in methane requires a net heat input of 105 kcal/mol to be broken at 25 ºC.
  - Table 5.3 lists energies for many bond types
- Changes in bonds can be used to calculate net changes in heat

Calculation of an Energy Change from Bond Dissociation Energies

- Addition of Cl-Cl to CH_4 (Table 5.3)
- Breaking: C-H D = 438 kJ/mol
  Cl-Cl D = 243 kJ/mol
- Making: C-Cl D = 351 kJ/mol
  H-Cl D = 432 kJ/mol

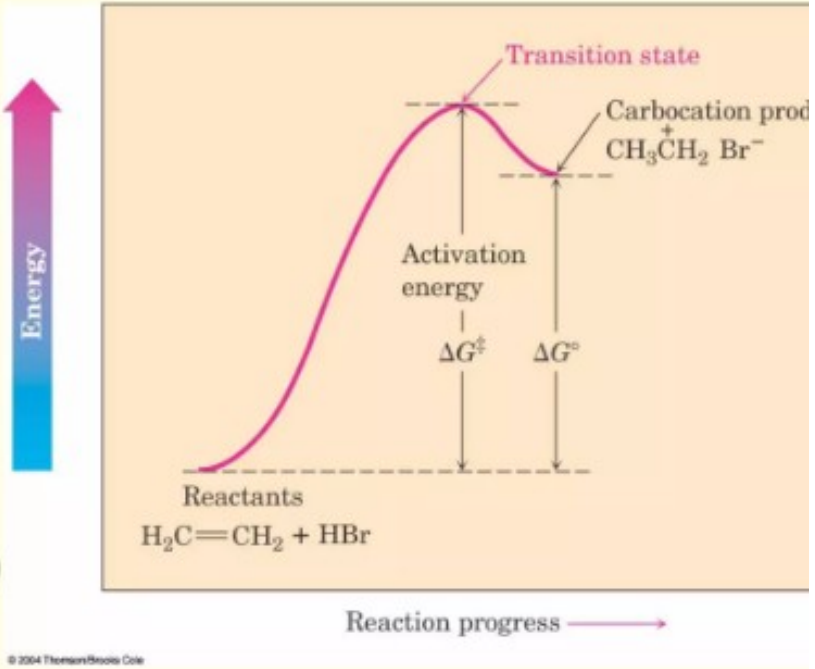
Energy of bonds broken = 438 + 243 = 681 kJ/mol

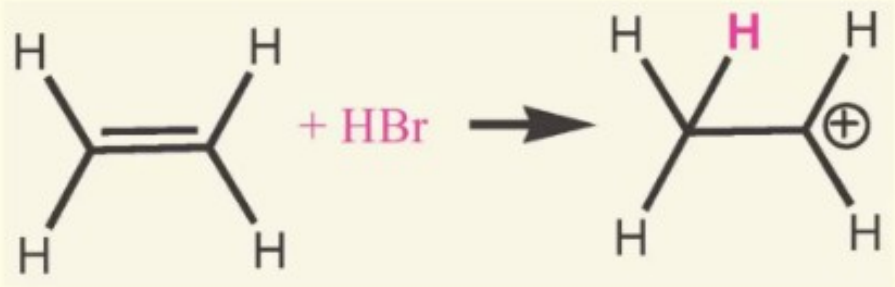
Energy of bonds formed = 351 + 432 = 783 kJ/mol

ΔH^o = 681 – 783 kJ/mol = -102 kJ/mol

6.9 Describing a Reaction: Energy Diagrams and Transition States

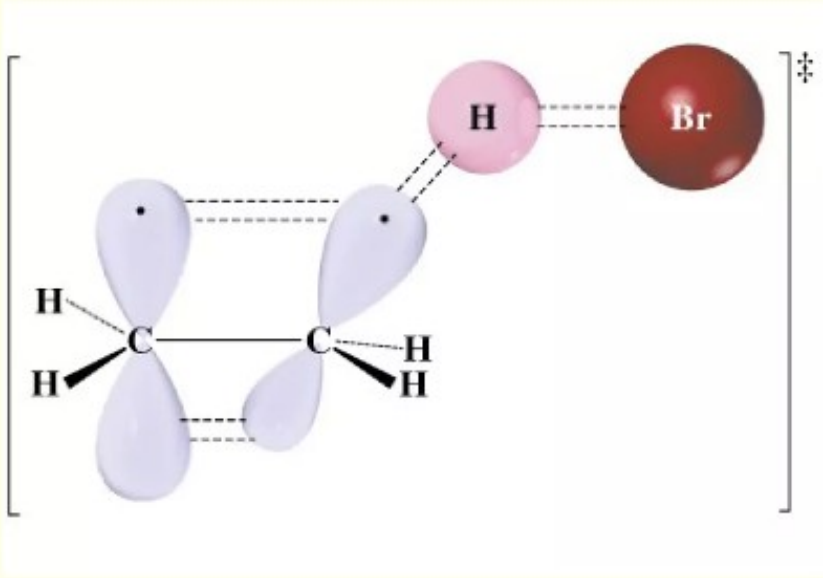
- The highest energy point in a reaction step is called the **transition state**
- The energy needed to go from reactant to transition state is the **activation energy** (ΔG)





First Step in Addition

- In the addition of HBr the (conceptual) transition-state structure for the first step
- The π bond between carbons begins to break
  - The C–H bond begs to form
  - The H–Br bond begins to break

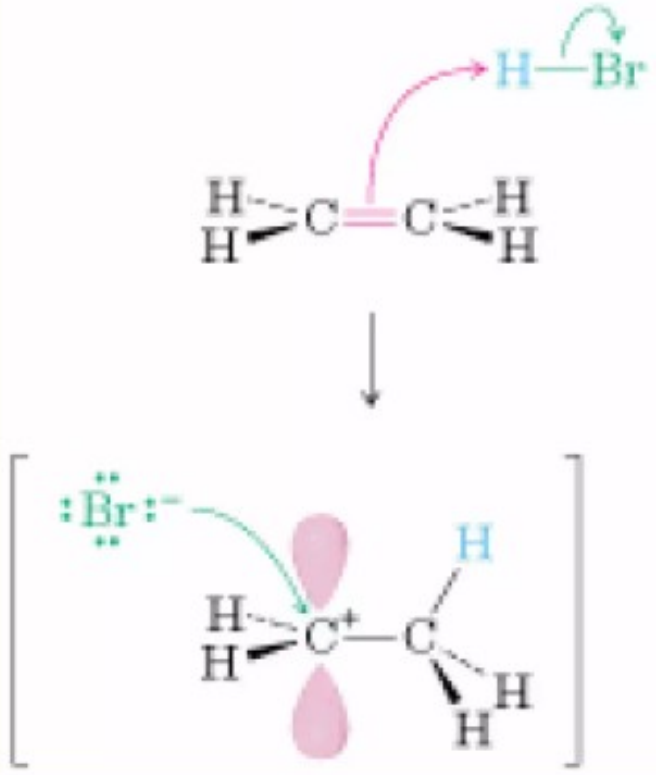


6.10 Describing a Reaction: Intermediates

- If a reaction occurs in more than one step, it must involve species that are neither the reactant nor the final product
- These are called **reaction intermediates** or simply "intermediates"
- Each step has its own free energy of activation
- The complete diagram for the reaction shows the free energy changes associated with an intermediate

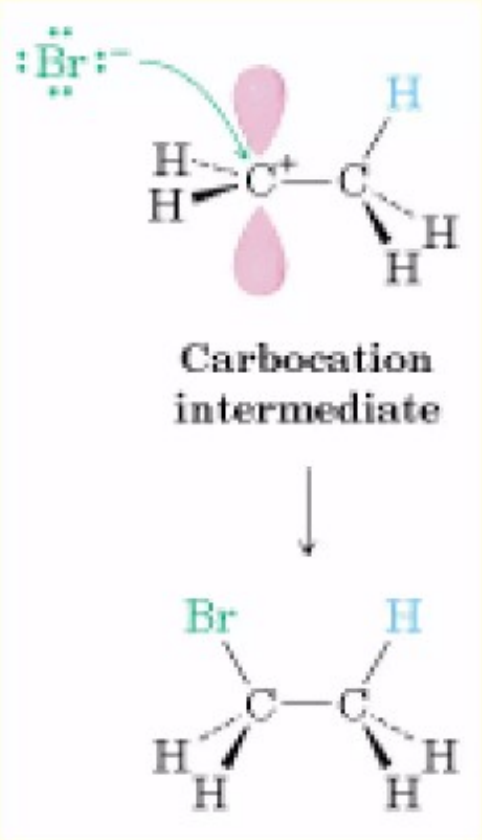
Formation of a Carbocation Intermediate

- HBr, a Lewis acid, adds to the π bond
- This produces an intermediate with a positive charge on carbon - a carbocation
- This is ready to react with bromide



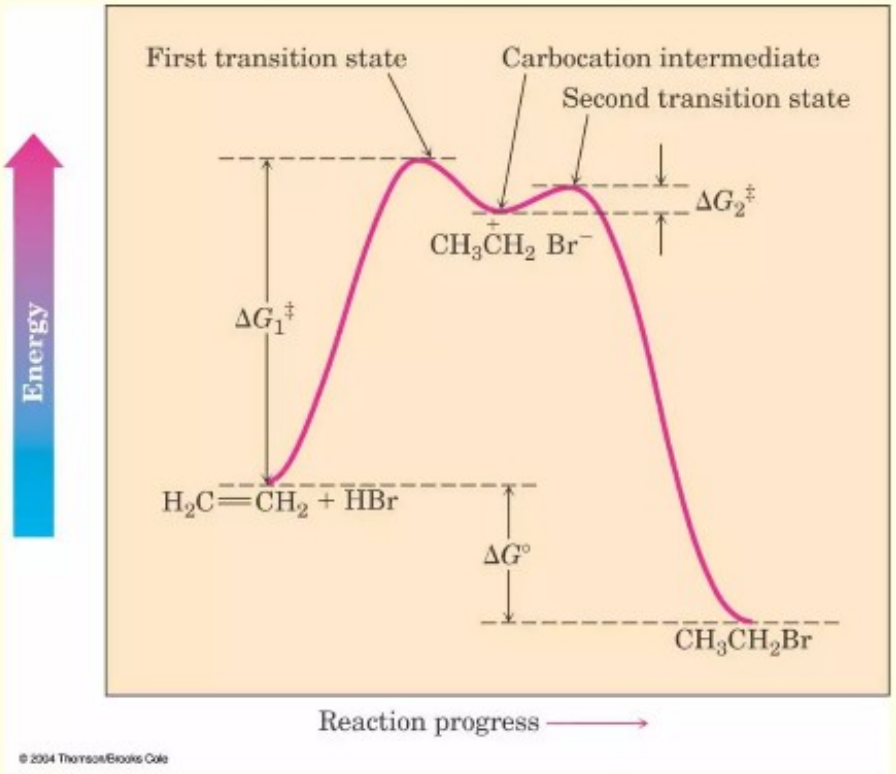
Carbocation Intermediate Reactions with Anion

- Bromide ion adds an electron pair to the carbocation
- An alkyl halide produced
- The carbocation is a reactive intermediate



Reaction Diagram for Addition of HBr to Ethylene

- Two separate steps, each with a own transition state
- Energy minimum between the steps belongs to the carbocation reaction intermediate.

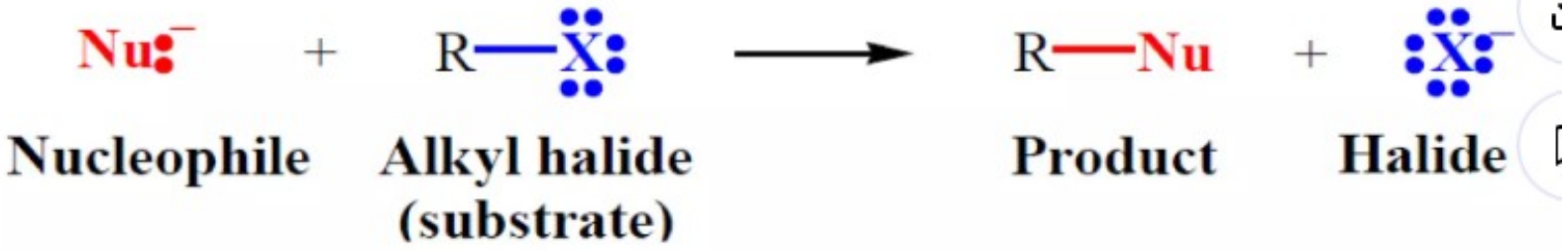


Biological Reactions

- Reactions in living organisms follow reaction diagrams too
- They take place in very controlled conditions
- They are promoted by catalysts that lower the activation barrier
- The catalysts are usually proteins, called enzymes
- Enzymes provide an alternative mechanism that is compatible with the conditions of life

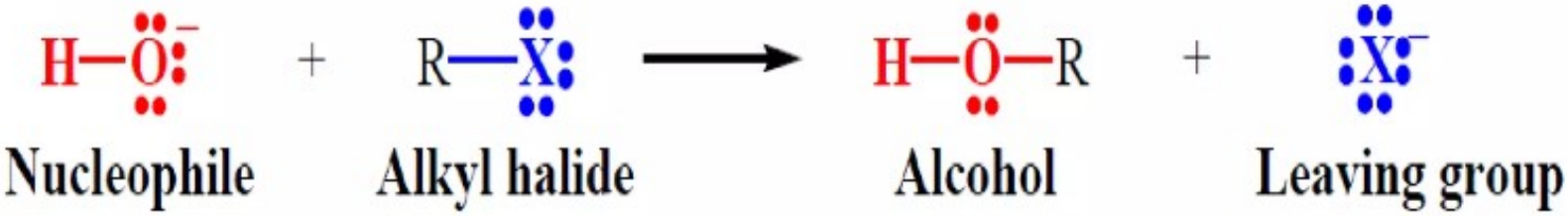
Nucleophilic Substitution Reactions

S_N1 and S_N2



- **A nucleophile, a species with an unshared electron pair (lone-pair electrons), reacts with an alkyl halide (substrate) by replacing the halogen substituent (leaving group).**
- **In nucleophilic substitution reactions, the C–X bond of the substrate undergoes *heterolysis, and the lone-pair electrons of the nucleophile is used to form a new* bond to the carbon atom.**

A **nucleophile is any negative ion or any neutra molecule that has at least one unshared electron pair-*General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion.***



- ***To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion.***
- **In alkyl halides the leaving group is the halogen substituent — it leaves as a halide ion.**
- **Because halide ions are relatively stable and very weak bases, they are good leaving groups.**

NUCLEOPHILIC SUBSTITUTION REACTION
AN S_N2 REACTION

- **The rate of the reaction depends on the concentration of methyl chloride and the concentration of hydroxide ion**
- **The reaction is second order overall.**
- **The reaction is first order with respect to methyl chloride and first order with respect to hydroxide ion**

Rate equation: $\text{Rate} \propto [CH_3Cl]\,[OH^-] \Rightarrow \text{Rate} = k\,[CH_3Cl]\,[OH^-]$

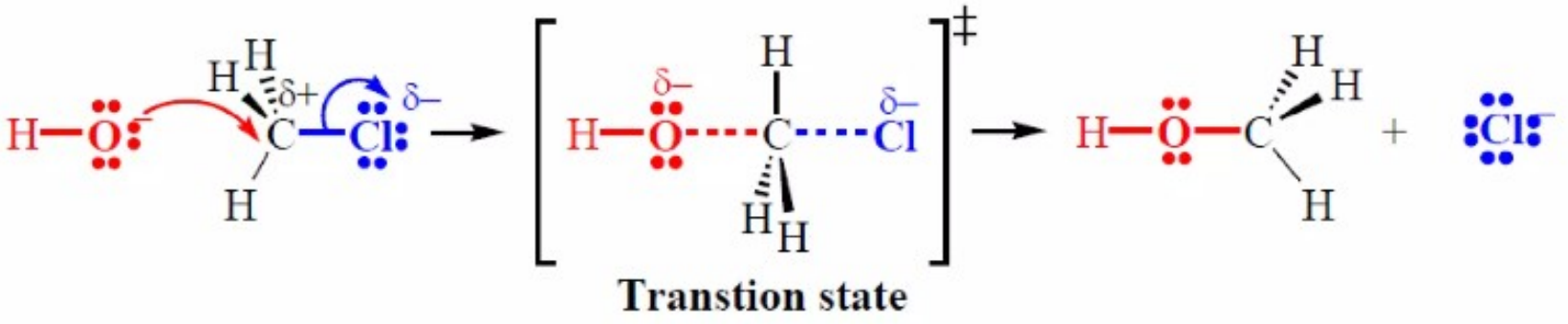
k is the rate constant.

MECHANISM FOR THE S_N2 REACTION

- **The nucleophile attacks the carbon bearing the leaving group from the back side.**
- **The bond between the nucleophile and the carbon atom is forming, and the bond between the carbon atom and the leaving group is breaking.**
- **The configuration of the carbon atom becomes inverted during S_N2 reaction.**
- **Because bond formation and bond breaking occur simultaneously in a single transition state, the S_N2 reaction is a *concerted reaction.***

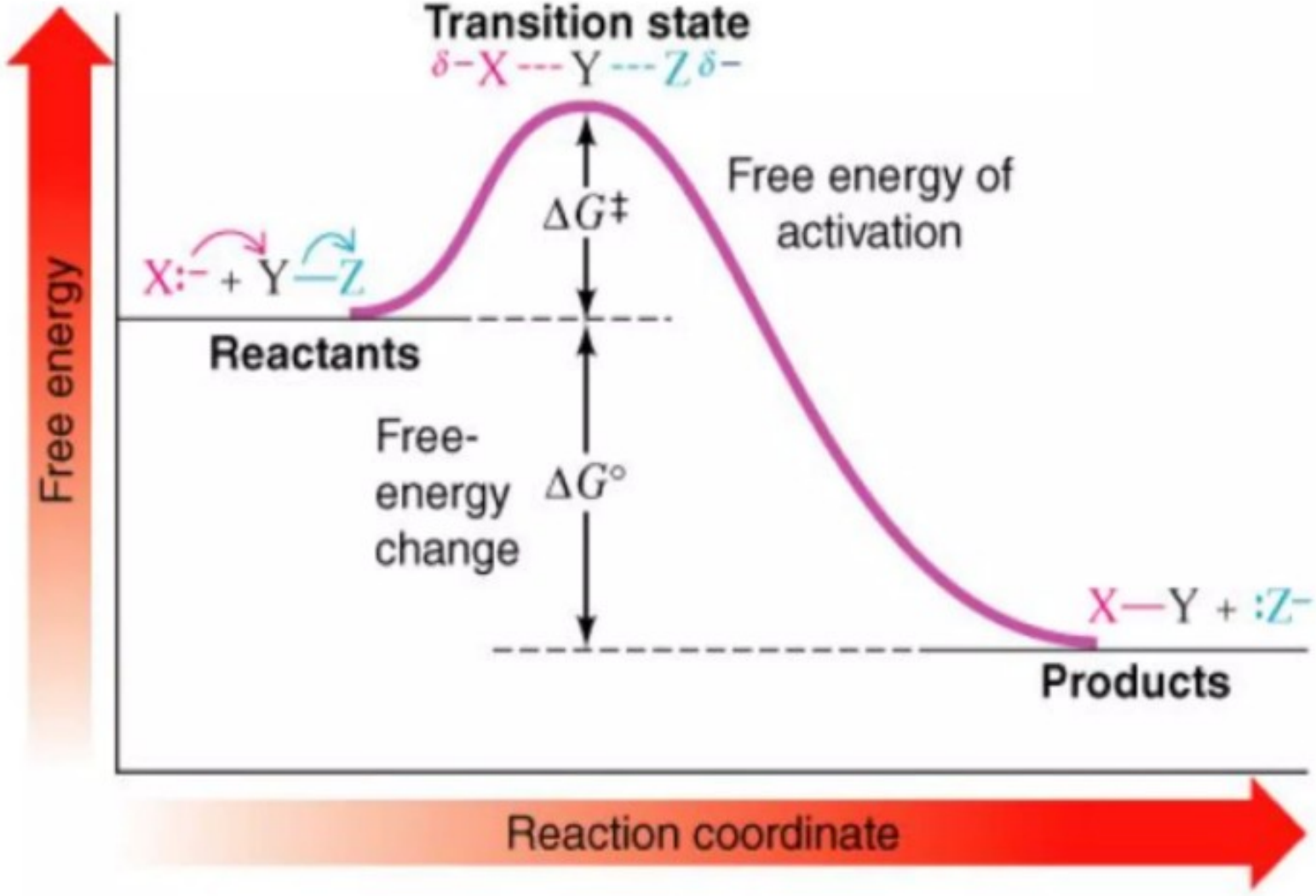
Mechanism

Mechanism:

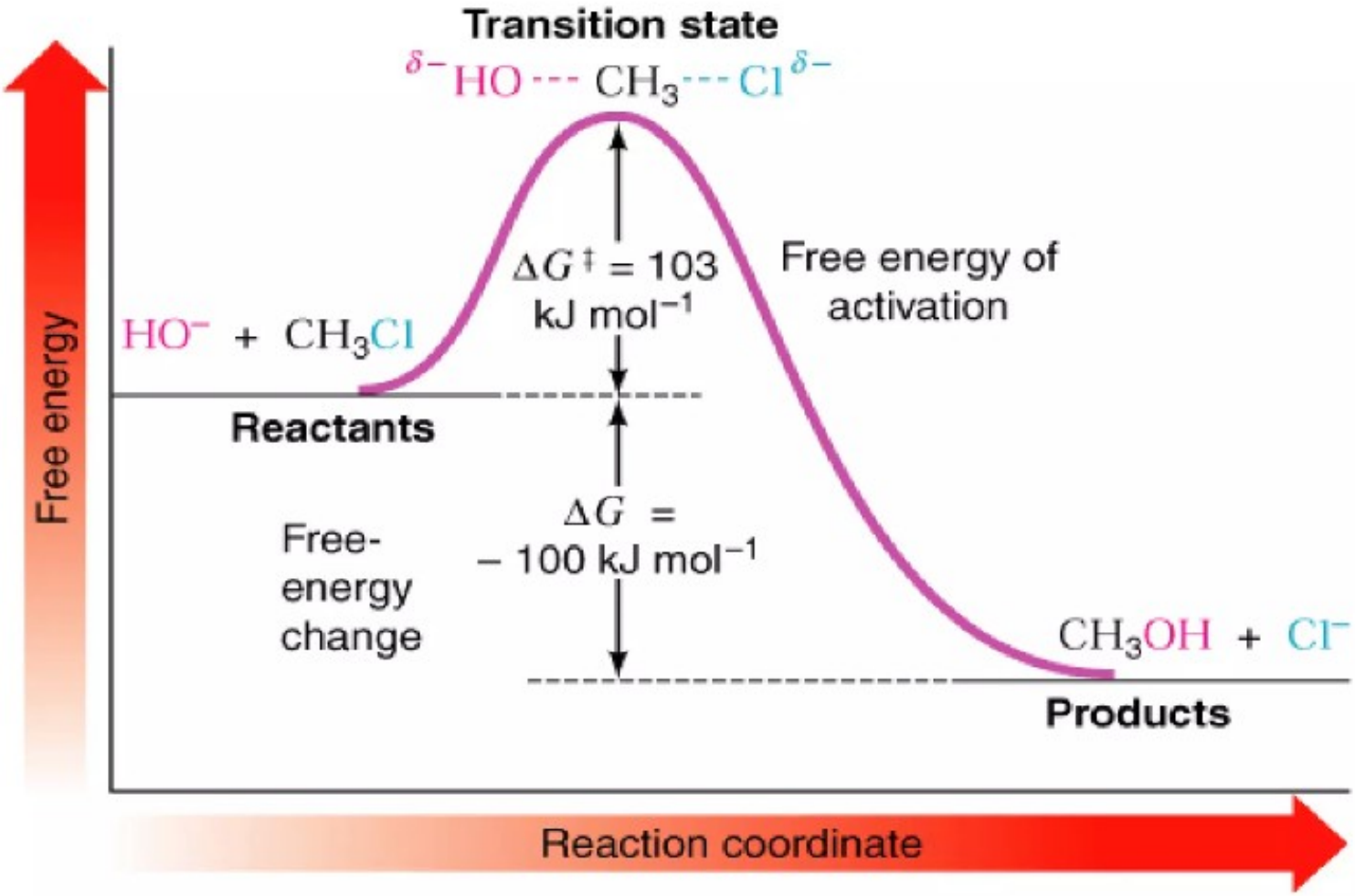


Transtion state

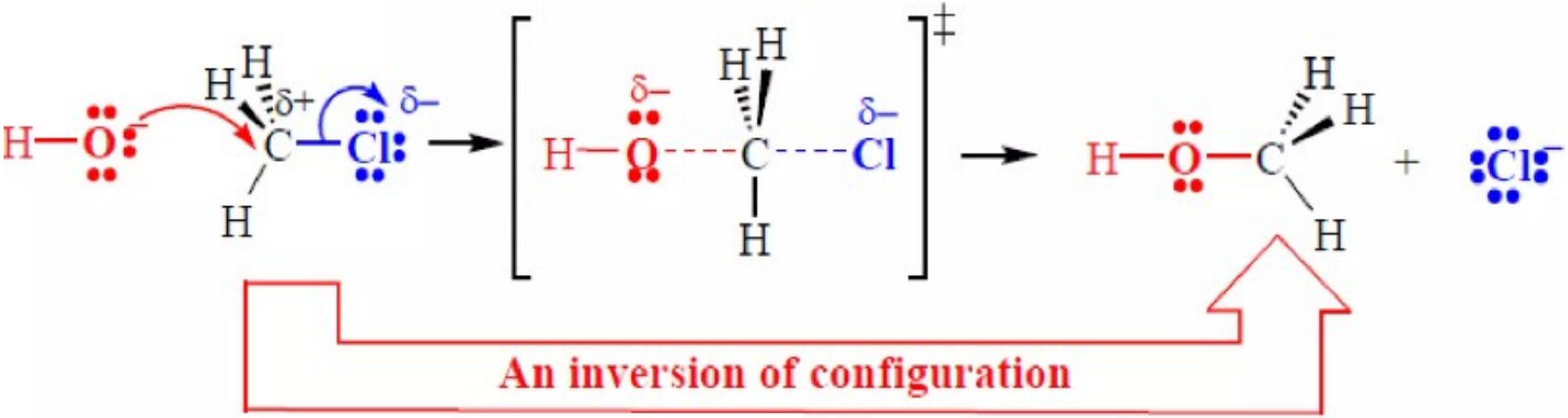
Free Energy Diagram



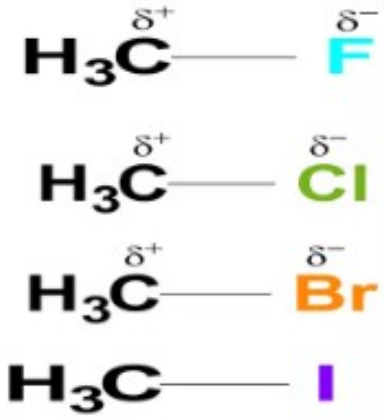
For Methanol



Stereo Chemistry



Reactions of Alkyl Halides (R-X): [SN1, SN2 reactions]



ΔEN (F-C) = (4.0 – 2.5) = 1.5

ΔEN (Cl-C) = (3.0 – 2.5) = 0.5

ΔEN (Br-C) = (2.8 – 2.5) = 0.3

ΔEN (I-C) = (2.5 – 2.5) = 0.0

The α-carbon in an alkyl halide is electrophilic (electron accepting) for either or both of two reasons…

a) the C to X (F, Cl, Br) bond is polar making carbon δ+

b) X (Cl, Br, I) is a leaving group

decreasing basicity, increasing stability

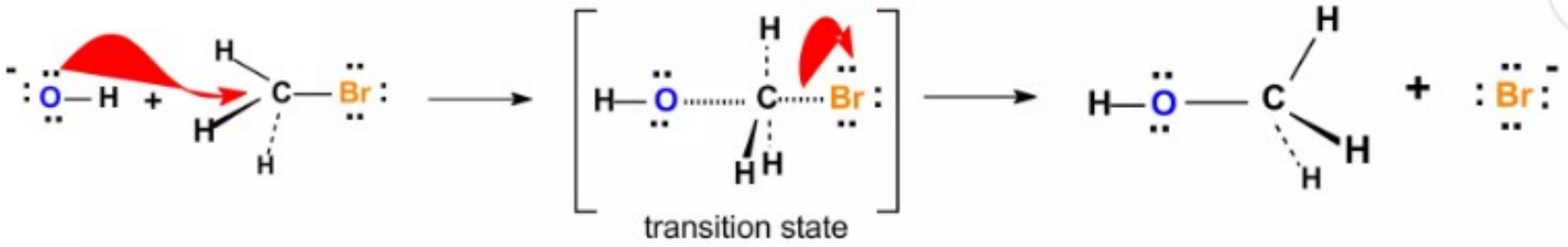
The best leaving groups are the weakest bases.

pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7
I^-	Br^-	Cl^-	F^-	HO^-
30,000	10,000	200	1	0

The poorest leaving groups are the strongest bases.

increasing leaving ability

2nd Order Nucleophilic Substitution Reactions, i.e., S_N2 reactions



The rate of an S_N2 reaction depends upon 4 factors:

1. The nature of the substrate (the alkyl halide)
2. The power of the nucleophile
3. The ability of the leaving group to leave
4. The nature of the solvent

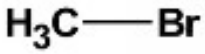
1. Consider the nature of the substrate:

- Unhindered alkyl halides, those in which the back side of the α-carbon is not blocked, will react fastest in S_N2 reactions, that is:

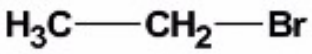
  Me° >> 1° >> 2° >> 3°

- While a methyl halides reacts quickly in S_N2 reactions, a 3° does not react. The back side of an α-carbon in a 3° alkyl halide is completely blocked.

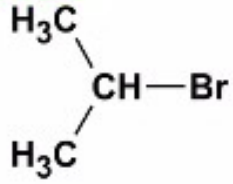
Effect of nature of substrate on rate of S_N2 reactions:



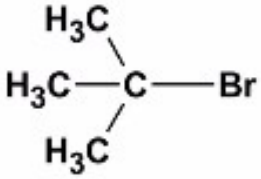
methyl bromide



ethyl bromide

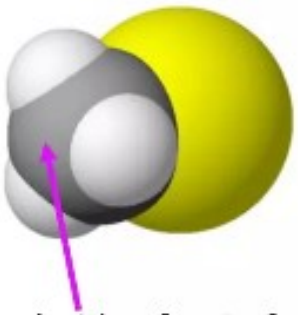


isopropyl bromide

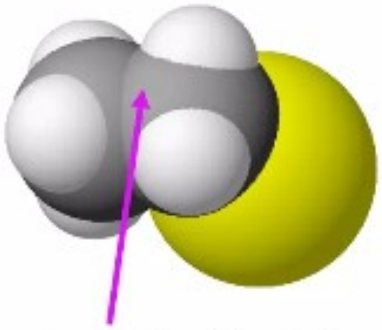


t-butyl bromide

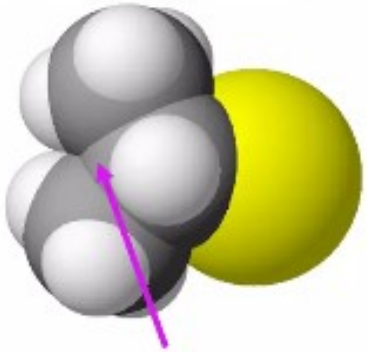
SPACE FILLING MODELS SHOW ACTUAL SHAPES AND RELATIVE SIZES



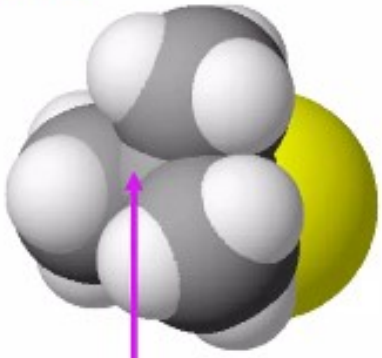
Back side of α-C of a methyl halide is unhindered.



Back side of α-C of a 1° alkyl halide is slightly hindered.



Back side of α-C of a 2° alkyl halide is mostly hindered.



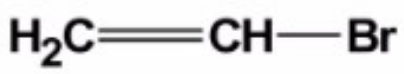
Back side of α-C of a 3° alkyl halide is completely blocked.

- **Me° >> 1° >> 2° >> 3°**

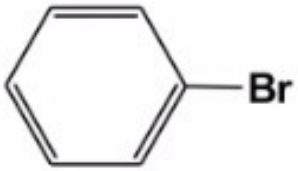
decreasing rate of *S_N2 reactions*

Effect of the nucleophile on rate of S_N2 reactions:

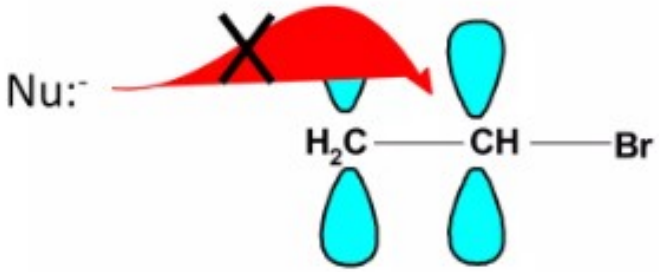
- **The α-carbon in vinyl and aryl halides, as in 3° carbocations, is completely hindered and these alkyl halides do not undergo S_N2 reactions.**

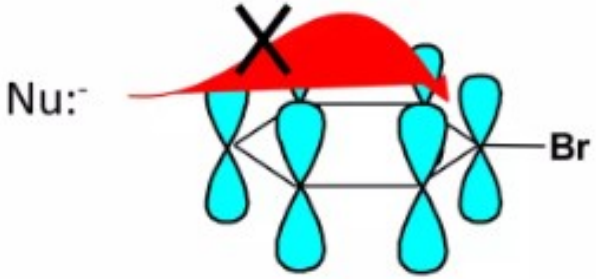


vinyl bromide



bromobenzene





The overlapping p-orbitals that form the π-bonds in vinyl and aryl halides completely block the access of a nucleophile to the back side of the α-carbon.

Effect of nature substrate on rate of S_N2 reactions:

Consider the power of the nucleophile:

- The better the nucleophile, the faster the rate of S_N2 reactions.
- The table below show the relative power or various nucleophiles.
- The best nucleophiles are the best electron donors.

Reactivity	Nu:$^-$	Relative Reactivity
very weak	HSO_4^-, $H_2PO_4^-$, RCOOH	< 0.01
weak	ROH	1
	HOH, NO_3^-	100
fair	F^-	500
	Cl^-, $RCOO^-$	20×10^3
	NH_3, CH_3SCH_3	300×10^3
good	N_3^-, Br^-	600×10^3
	OH^-, CH_3O^-	2×10^6
very good	CN^-, HS^-, RS^-, $(CH_3)_3P$:, NH_2^- ,RMgX, I^-, H^-	$> 100 \times 10^6$

increasing

• 3. Consider the nature of the leaving group:

- The leaving group usually has a negative charge
- ❑ Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.
- ❑ Weak bases are readily identified. They have high pKb values.

pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7	pKb = -2	pKb = -21
I^-	Br^-	Cl^-	F^-	HO^-	RO^-	H_2N^-
30,000	10,000	200	1	0	0	0

Increasing leaving ability

- ❑ Iodine (-I) is a good leaving group because iodide (I^-) is non basic.
- ❑ The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH^-) is a strong base.

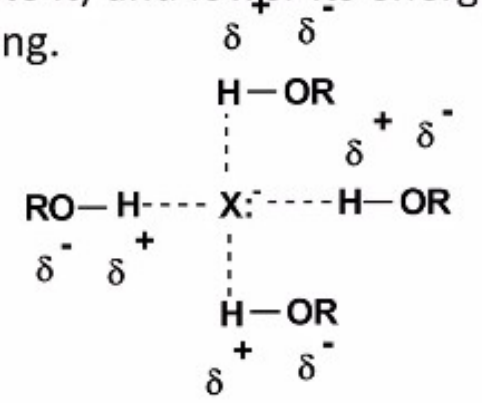
Effect of the solvent on rate of S_N2 reactions:

- **4. Consider the nature of the solvent:**

- **There are 3 classes of organic solvents:**

- **Protic solvents, which contain –OH or –NH_2 groups. Protic solvents slow down S_N2 reactions.**
- **Polar aprotic solvents like acetone, which contain strong dipoles but no –OH or –NH_2 groups. Polar aprotic solvents speed up S_N2 reactions.**
- **Non polar solvents, e.g., hydrocarbons. S_N2 reactions are relatively slow in non polar solvents.**

Protic solvents (e.g., H_2O, MeOH, EtOH, CH_3COOH, etc.) cluster around the Nu:- (solvate it) and lower its energy (stabilize it) and reduce its reactivity via H-bonding.



A solvated anion (Nu:-) has reduced nucleophilicity, reduced reactivity and increased stability

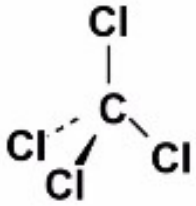
A solvated nucleophile has difficulty hitting the α-carbon.

Effect of the solvent on rate of S_N2 reactions:

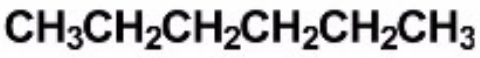
•Non polar solvents (benzene, carbon tetrachloride, hexane, etc.) do not solvate or stabilize nucleophiles.

– S_N2 reactions are relatively slow in non polar solvents similar to that in protic solvents.

benzene



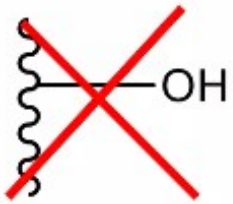
carbon tetrachloride

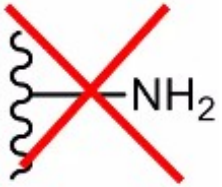


n-hexane

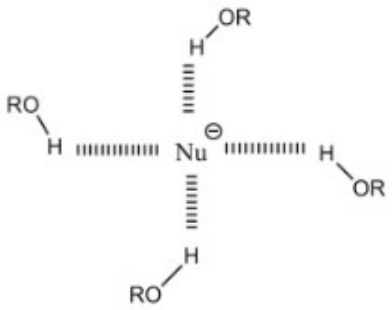
Solvent Effect for S_N2 reactions

- Requires a polar, aprotic solvent…
- NO alcohols or amines





Why…because hydrogen bonding with the nucleophile can occur…slowing down the reaction



S_N2 Conditions Summary

- 1) Substrate (methyl > primary > secondary >> tertiary)
- 2) Nucleophile (negative charge > neutral)
- 3) leaving group (Y) (Y stabilizes a negative charge)
- 4) solvent (needs to be polar and aprotic)